REMARKS

Applicants acknowledge with appreciation the time and courtesies extended by the examiners toward Applicants' representatives during a telephone interview conducted with Applicants' representative on Thursday, December 9, 2004. The examiners' insights and comments have advanced the prosecution of the case. In particular, the outstanding 35 U.S.C. §103(a) rejections were discussed and ways that Applicants' representative can achieve further clarity in responding to the examiners' outstanding rejections.

Applicants address the examiner's remarks in the order presented in the Office Action (dated July 14, 2004). All claim amendments are made without prejudice and do not represent acquiescence in any ground of rejection.

STATUS OF THE CLAIMS

Claims 13, 18, and 19 are currently pending. Claim 13 is amended. After entry of this amendment, Claims 13, 18, and 19 will be pending. Support for the amendments to claim 13 can be found in the claims as originally filed and throughout the application as filed. Additional support for "Human Immunodeficiency Virus" can be found, for example, on page 21, at lines 16-18. Additional support for the phrase "phenotypic" resistance can be found beginning on page 15 at line 1 through page 19 at line 12. Exemplary support within these pages can be found on page 15, lines 3-8. Further support for "wherein the phenotypic resistance is expressed as the fold-change in the IC_{50} or IC_{90} values of one or more therapeutic agents", can be found, for example, on page 15, lines 1-8. No new matter is added by the amendments. Additional support for the amendments can be found in Table 4 on page 33.

Claims 13, 18, and 19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ioannidis *et al.*, 1998, *American Journal of Epidemiology* 147: 464-471, in view of Harrigan *et al.*, 1999, *AIDS* 13: 1863-1871.

REJECTIONS UNDER 35 U.S.C. §103(A)

Claims 13, 18, and 19 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ioannidis *et al.*, 1998, *American Journal of Epidemiology* 147: 464-471, in view of Harrigan *et al.*, 1999, *AIDS* 13: 1863-1871. Applicants have amended claim 13 for

greater clarity and consistency of claims language. Applicants also respectfully traverse in part.

According to the examiner, the instant claims are drawn to a neural network for predicting resistance of HIV to a therapeutic agent. The examiner characterizes Ioannidis *et al.* as teaching the use of neural networks in modeling complex immunogenetic associations of disease. In particular, the examiner stated that loannidis *et al.* teach a feed-forward neural network with back propagation (claim 1), including a training process where weights are adjusted to minimize error (page 465, column 2). The examiner further states that the network is composed of several layers of neurons, including an input layer, one or more hidden layers, and an output layer (claims 18 and 19).

While Ioannidis *et al.* do teach the use of a neural network for allele prediction in AIDS, the examiner notes that Ioannidis *et al.* do not specifically teach the prediction of resistance of HIV to a therapeutic agent. For this purpose, the examiner uses Harrigan *et al.* as teaching drug resistance determination.

According to the examiner, Harrigan *et al.* teach phenotype and genotype assessment of resistance of 10 different antiviral agents. This baseline drug resistance method was predictive of resistance of HIV to ritonavir and saquinavir. Drug resistance phenotype was predictive of poor virological response to this particular dual protease inhibitor combination (page 1863). The examiner states that the conclusion drawn was that baseline resistance to ritonavir or saquinavir or both was associated with poor antiviral response. The data suggest, according to the authors, that the measurement of drug resistance *may* assist in optimizing antiretroviral therapy in the clinic (page 1863) (emphasis added by Applicants). Therefore, the examiner takes the position that it would have been *prima facie* obvious to one of skill in the art at the time of the invention to employ the neural network of loannidis *et al.* for the assessment of predicting drug resistance of HIV, as allegedly is characterized to have been done by Harrigan *et al.*

Specifically the examiner points to the motivation to use a neural network is provided in the statement by Ioannidis *et al.*, which says, "neural networks could be trained to recognize genetic patterns in conjunction with associated clinical outcomes, and their performance in modeling these complex associations in a training set was superior to logistic regression models." (page 469, column 1). According to the examiner, Harrigan *et al.* use

logistic regression in their assessment of baseline resistance; however, it would have been obvious to improve the accuracy of the resistance testing by using the neural network of Ioannidis *et al.* for the reasons set forth above. Applicants traverse for the following reasons.

Claims cannot be found obvious unless the prior art itself suggests the desirability of the combination. *Berghauser v. Dann,* 204 U.S.P.Q. 393 (D.D.C. 1979); *ACS Hospital Systems Inc., v. Montefiore Hospital,* 221 U.S.P.Q. 929 (Fed. Cir. 1984). There must be something in the prior art that would have motivated persons of ordinary skill to make the combination. *In re Stencel,* 4 U.S.P.Q.2d 1071 (Fed. Cir. 1987), *accord, Ex parte Marinaccio*, 10 U.S.P.Q.2d 1716 (Pat. Off. Bd. App. 1989)(combining references is improper absent some teaching, suggestion, or motivation for the combination in the prior art).

Obviousness cannot be established by merely showing that it would have been possible for a person of ordinary skill to combine or modify teachings of the prior art. The prior art must suggest the desirability of the claimed invention. MPEP 2143.01. Moreover, there must be affirmative evidence that such a person would have been **"impelled"** to make the combination. *Ex parte Levengood*, 28 U.S.P.Q.3d 1300, 1302 (Pat. Off. Bd. App. 1993)(citations omitted). As is stated in M.P.E.P. § 2143, three criteria must be met to establish prima facie obviousness:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Moreover, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention when there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one ordinary skill in the art. MPEP § 2143.01

Here, a *prima facie* case of obviousness has not been established, at least because there is no suggestion or motivation to modify the references. As will be made clear below,

the cited references do not teach the claimed invention and even if combined, one of skill would not be able to arrive at the subject matter as claimed in claim 13 or disclosed in the instant specification.

Ioannidis *et al.* is considered to constitute the closest prior art, because it employs neural networks to correlate immunogenetic markers with AIDS disease progression.

Ioannidis *et al.* employ:

- as input: human leukocyte antigen (HLA) data on class I and class II alleles and TAP variants for the training and validation of the neural network; and
- as output: a binary outcome - one or zero, for the progression to AIDS within 6 years or not.

The objective problem which the current invention seeks to solve is the provision of a computational tool that can recognize complex genetic patterns of resistance within the therapy dimension, *i.e.*, individual and combination of base mutations, which confer resistance, cross-resistance, susceptibility and cross-susceptibility to one or more of the antivirals or other therapeutic agents available in the market. This problem is now solved by the invention as addressed in claim 13.

The difference of claim 13 with Ioannidis *et al.* is the training data set, the testing data set and the query inputs and outputs which correspond to one or more genetic mutations (input) and their paired phenotypic resistance change (output).

The teaching disclosed by Harrigan *et al.* makes actual correlations of genotypes and/or phenotypes with clinical response, expressed in logarithmic viral load values (copies of RNA per mL). To achieve this correlation, Harrigan *et al.* employ a univariate and multivariate logistic regression. The approach by Harrigan *et al.* is further limited in that it predicts clinical response on the administration of ritonavir and saquinavir only, which are both protease inhibitors. Conversely, the present invention is able to predict resistance (***not*** clinical response as taught by Harrigan *et al.* and discussed in further detail below) to any antiviral compound or therapeutic agent, be it a protease inhibitor, a reverse-transcriptase inhibitor, an entry inhibitor, and the like, or any combination thereof.

Applicants now discuss the issue of "resistance" in further detail below.

There are three types of resistance (see www.aids.org):

(1) Clinical resistance: which measures the symptoms of HIV disease or the progression into AIDS and related illnesses in a given patient. It is normally expressed as viral load (number of HIV RNA copies/mL) or as CD4 counts.

(2) Phenotypic resistance: which measures the HIV replication activity in a test tube when antiviral drugs or other therapeutic agents are added. It is expressed as IC_{50} or EC_{50} (concentration of antiviral needed to inhibit 50% of the total virus population in a tube).

(3) Genotypic resistance: which is the mutation(s) in the genetic sequence of HIV that are associated to drug resistance. It is expressed as an amino acid or combination of amino acids and a number indicating their position in the HIV genome, *e.g.*,73S (thus at position 73, the original aminoacid has mutated to serine; 30N 77I (at position 30 the original aminoacid has mutated to asparagine, and at position 77, the original amino acid has mutated to isoleucine).

Harrigan *et al.* teach correlating genotypic and/or phenotypic resistance with clinical resistance (as defined above). Ioannidis *et al.*, on the other hand, correlates HLA genotypic sequences with clinical resistance, expressed as 0 (no disease progression to AIDS within 6 years) or 1 (disease progression to AIDS within 6 years).

Applicants' instant invention, conversely, correlates genotypic resistance with phenotypic resistance. Taking an HIV sequence (*e.g.*, ACTG.....) as input, it is able to calculate an IC_{50} value against one or more antivirals or other therapeutic agents. See, *e.g.*, Table 7 in the instant specification.

Even if Ioannidis *et al.* were to be combined with Harrigan *et al.*, one of skill in the art would not arrive at the subject matter as claimed in claim 13 or disclosed in the instant specification. Both prior art documents, while employing different computational approaches (neural networks and logistic regression respectively), are both focused on correlating genotypic and/or phenotypic (in the case of Harrigan *et al.*) markers with clinical outcomes, be it disease progression or viral load changes.

On the provision of a computational tool that can recognize complex genetic patterns of resistance within the drug dimension, both Ioannidis *et al.* and Harrigan *et al.* are completely silent and therefore the one of skill in the art would not be able to recognize the alleged technical problem starting from the disclosure of any one of the prior art documents.

Although Applicants continue to traverse this rejection, in an effort to expedite prosecution of this application, Applicants have amended claim 13 as discussed above to a method for predicting phenotypic resistance of Human Deficiency Virus (HIV) to a therapeutic agent. Further, amended claim 13 now reads, in part, as a method for training a neural network on a training data set, providing a determined HIV genetic sequence from a patient, and predicting the phenotypic resistance of HIV to the therapeutic agent by inputting the determined genetic sequence into the trained neural network which computes the predicted phenotypic resistance of HIV to a therapeutic agent, wherein the phenotypic resistance is expressed as the fold-change in the IC_{50} or IC_{90} values of one or more therapeutic agents.

For at least these reasons, Applicants respectfully submit that the rejection of the pending claims is improper. Claim 13, as amended, is therefore inventive over the prior art and is considered patentable. Claims 18 and 19 depend from claim 13 and are therefore inventive over the prior art for the same reasons.

Without acceding to the propriety of the rejection of pending claims 13, 18 and 19 under 35 U.S.C. § 103, Applicants respectfully request reconsideration of the claims as amended. For these reasons, Applicants request the examiner to withdraw the rejection of pending claims 13, 18, and 19 under 35 U.S.C. § 103.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants submit that this application is now in condition for allowance.

Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested. If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Respectfully submitted,

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